## REMARKS

Claims 1-42 are pending. Claims 1-38 are under examination and claims 39-42 are withdrawn from consideration. Claims 1, 10 and 19 are amended herein. Accordingly, claims 1-42 will remain pending in the application.

Amendment and cancellation of the claims are not to be construed as acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims, in one or more subsequent patent applications.

Applicants respectfully traverse all the rejections/objections of record as set forth in the instant Office Action. However, without in any way acquiescing to the rejections/objections and in order to expedite prosecution of the application, the claims have been amended as set forth above, thereby obviating all the rejections/objections of record. Applicants submit that claims 1-38 as presented herein are in condition for allowance.

### Support for the Amendments

Support for the amendments is found throughout the specification and claims as originally filed. For example, support for the amendment of claim 1, which now recites "a protein product of the AGA2 gene" is found at claim 5 as originally filed; support for the amendment of claim 10, which now recites "encodes a polypeptide," is found, for example, at page 22, lines 8-10; and support for the amendment of claim 19, which replaces "SPA" with "scintillation proximity assay" is provided, for example, at page 46, line 34. No new matter has been added.

### Rejection under 35 U.S.C. § 112, second paragraph

Claims 9, 10 and 19 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner asserts that claims 9 and 10 are indefinite for reciting the term "reporter gene." Applicants respectfully disagree.

Applicants note that the reporter gene is not a part of the cell recited in claim 1. As is clear from claim 6, the cell recited in claim 1 is incubated with detector molecule conjugated with a reporter moiety. Claim 9 recites that the reporter moiety is a reported gene. The term "reporter gene" is defined in the instant application at page 13, lines 23-33, where Applicants state that the term "reporter gene" is "used interchangeably herein to refer to an indicator gene operatively linked to at least one transcriptional regulatory sequence." To more particularly define the claimed invention, claim 10 has been amended to clarify that the reporter gene recited in claim 9 encodes a polypeptide of claim 10.

Claim 19 is rejected as indefinite for reciting the term "SPA." This rejection is overcome by the present amendment, which replaces "SPA" with "scintillation proximity assay."

**Rejection under 35 U.S.C. § 102**

Claims 1-4, 35 and 38 are rejected under 35 U.S.C. § 102(e) as being anticipated by Trueheart, *et al.*, (U.S. Patent No. 6,159, 705, which was filed on September 24, 1997; hereinafter "Trueheart"). Without in any way acquiescing to the rejection, this rejection is rendered moot by the present amendment, which was made solely to expedite prosecution. Claim 1 has been amended to recite that "cell surface presentation of a detectable signal comprising ***a protein product of the AGA2 gene*** is induced upon activation of said signal transduction pathway". Trueheart fails to teach or suggest a compound-screening assay that employs a detectable signal comprising an Aga2 protein product. Therefore, Trueheart does not anticipate claim 1 and claims 2-4, 35 and 38 depending therefrom because it does not teach each and every element of the claims. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(e) rejection.

**Rejection under 35 U.S.C. § 103**

Claims 5, 11, 14, 16, and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trueheart in view of Cappellaro, *et al.*, (EMBO J. 10:4081-4088, 1991; hereinafter "Cappellaro"). Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Cappellaro and Wojciechowicz (Mol. Cell Biol. 13:2554-2563, 1993).

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Cappellaro, Wojciechowicz, and Wu, *et al.*, (Analytical Biochemistry 249:29-36, 1997; hereinafter "Wu"). Claims 18-20 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Cappellaro, Alberts, *et al.*, (molecular biology of the Cell, 2nd Edition, Garland Publishing, Inc., 1989; hereinafter "Alberts") and Nare, *et al.*, (Analytical Biochemistry, 267:390-396, 1999; hereinafter "Nare"). Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Cappellaro, Alberts, and Nare; and as applied to claims 18-20, 23, and 24 further in view of Wojciechowicz (Mol. Cell. Biol. 13:2554-2563, 1993). Claims 6, 9-11, and 14 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Alberts. Claims 7 and 9 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart in view of Alberts, and as applied to claims 6, 9-11, and 14, further in view of Wojciechowicz. Claim 26 is rejected under 35 U.S.C. as being unpatentable over Trueheart in view of Roy (Mol. Cell. Biol. 11:4196-4206, 1991); claims 27-29 and 32-34 are rejected under 35 U.S.C. 103(a) as unpatentable over Trueheart in view of Roy and further in view of Alberts and Nare. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Trueheart in view of Roy and Alberts, and as applied to claims 27-29, 32, and 33, further in view of Wojciechowicz. Claims 36 and 37 are rejected under 35 U.S.C. 103(a) in view of Reppert.

Applicants respectfully disagree and traverse the rejection for the reasons set forth below. Applicants traverse the rejection with respect to pending claim 1, which has been amended to recite "an AGA2 protein product," as previously recited by claim 5. The rejection is moot as to claim 5, which has been cancelled.

To establish a *prima facie* case of obviousness over the cited references, the Examiner must show that three criteria are met. First, the prior art reference must teach or suggest all the claim limitations. Second, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Finally, there must be a reasonable expectation of success. M.P.E.P. 2143. It is not enough that the references ***might*** have been combined to achieve the claimed invention.

The standard for obviousness requires a suggestion that the references ***should*** be combined and an expectation that the combination would operate ***successfully***.

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art . . . ***Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.*** *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1429 (Fed. Cir. 1988) (Emphasis added.)

The burden is on the Examiner to establish that the cited references provide the requisite motivation to combine and a reasonable expectation of success. M.P.E.P. 2142. In the absence of some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074.

Applicants now address the rejection with respect to each of the cited references.

*Trucheart*

The instant claims are directed to screening methods that feature cell surface presentation of a detectable signal comprising a protein product of the AGA2 gene, which is induced upon activation of a signal transduction pathway. Applicants were the first to appreciate that the protein product of an Aga2 gene could be used as a read-out for compound screening. As described at page 17, lines 12-25, the method involves contacting a yeast cell expressing a heterologous receptor with a test compound. If the compound is reactive with the receptor, Aga2 protein expression is increased. Thus, the amount of Aga2 protein expression on the cell surface is indicative of the ability of the test compound to activate the receptor expressed by the cell. The Aga2 protein is detected by identifying the specific interaction of the protein with a detector molecule conjugated with a reporter moiety. The readout from the reporter moiety indicates the presence or absence of the Aga2 protein, which provides a measure of the activity of the pheromone response pathway to stimulation of the receptor by the test compound.

The present invention is readily distinguishable from that described by Trueheart. As acknowledged by the Examiner, "Trueheart et al. fail to teach (1) the use of the protein product of Aga2 gene as a detectable signal." (Office Action mailed February 22, 2006, page 4, third paragraph.).

Trueheart failed to recognize as Applicants did that the Aga2 protein could be used in compound screening methods. There is nothing in Trueheart that would motivate one of ordinary skill in the art to select the Aga2 protein as a signal of activation of a signal transduction pathway. Moreover, there is nothing in Trueheart suggesting a problem with the screening assays disclosed therein such that one of ordinary skill in the art would be motivated to seek an alternative signaling paradigm. Furthermore, it is not sufficient that the method of Trueheart could be modified to include the use of Aga2. There is no express teaching or suggestion that the assay of Trueheart ***should*** be modified to include the use of Aga2 as a readout.

*Cappellaro*

The Examiner seeks to remedy the deficiencies of Trueheart by citing Cappellaro, which provides a description of the DNA sequence of the α-agglutinin binding fragment and a structure-function analysis of the active region of α-agglutinin that is required for a-α agglutinin complex formation. The Examiner asserts that it would have been obvious for one skilled in the art to use the Aga2 protein product described by Capellaro as a detectable signal in the screening methods described by Trueheart. The Examiner states:

> One skilled in the art would have been motivate to do so because (1) activation of pheromone response pathway induces production of the protein product of AGA2 gene (a-agglutinin) that specifically reacts with and binds to α-agglutinin, (2) treatment of the cells with a reducing agent results in release the cell surface signal molecules (such as a-agglutinin), and (3) an fluorescing antibody offers a sensitive means for the detection of a signal, as taught by Cappellaro et al. (Office Action mailed Feb. 22, 2006, page 5, 1ST full paragraph)

Applicants respectfully disagree. Capellaro merely characterizes the active domain of Aga2. Capellaro plainly fails to teach or suggest ***any*** method of compound screening, much less adapting the compound screening methods described by Trueheart by employing the Aga2

protein product as a readout. "The mere fact that the prior art ***could*** be so modified would not have made the modification obvious unless the prior art suggested the ***desirability*** of the modification." (*In re Lucas*, 733 F2d 900, at 902).

It is not enough that the skilled artisan might have attempted such a modification. The prior art references must indicate that the modification ***should*** be made and if made that the modification would be ***successful***. As noted earlier, there is nothing in Trueheart suggesting a problem with the screening assays disclosed therein such that one of ordinary skill in the art would be motivated to seek an alternative signaling paradigm. Moreover, because Capellaro is silent as to screening assays and because there is nothing in Truehcart that would motivate one of ordinary skill in the art to seek a read out other than those disclosed in Truehcart, one of ordinary skill in the art would not be motivated to combine the references as suggested by the Examiner. Accordingly, the rejection of the claims as obvious over Trueheart in view of Capellaro should also be withdrawn.

*Wojciechowicz*

In addition, the Examiner rejects claims 12 and 13, which are directed to methods of compound screening using the Sag1 protein or a fragment thereof as a detector molecule, as obvious over Trucheart and Capellaro in view of Wojciechowicz. The Examiner asserts that it would have been obvious for the skilled artisan to use the Sag1 protein in methods of compound screening. Applicants respectfully disagree and traverse the rejection.

Trueheart and Capellaro are discussed above and those discussions are reiterated here. Wojciechowicz does not alleviate the deficiencies of Trueheart and Capellaro. Wojciechowicz uses structure-function analysis to define the domain of α-agglutinin that mediates binding between α- and a-agglutinin. Similar to Capellaro, Wojciechowicz fails to teach or suggest methods of compound screening.

As described in Applicants' specification, at page 4, line 25, to page 5, line 2, Applicants' invention provides cells that express a heterologous receptor that is functionally integrated into a signal transduction pathway in the cell, in which cell surface presentation of Aga2, which acts as a detectable signal, is induced upon activation of the signal transduction pathway. The level of expression of Aga2 is detected using a detection step that includes incubating the cell with a

detector molecule conjugated with a reporter moiety, where the detector molecule binds specifically to the detectable signal. Applicants' specification discloses that the Sag1 protein is an exemplary detector molecule that may be used in the methods of the invention (page 44, Example 3, under the heading "Detection of Endogenous Aga2 protein using the N-terminal Domain of the α-agglutinin Sag1 Protein."

The Sag1 gene encodes the Aga2 proteins natural binding partner, the yeast α-agglutinin protein contains amino acids 20-352 of the mature α-agglutinin protein (page 44, lines 12-14). Applicants found that Sag1 could be used to detect Aga2 in lieu of an Aga2 specific antibody. Furthermore, Applicants recognized that Sag1 is preferable to such antibodies given the high affinity of the Aga2/Sag1 interaction (page 44, line 10-13; and page 46, lines 5-11). Applicants discovered that when yeast cells expressing the ML1a receptor integrated in to the endogenous yeast signal transduction pathway were stimulated with melatonin Aga2 protein production was induced. The expression of Aga2 at the surface of the cells could be detected with $Sag1^{p21-352}$ with an $EC_{50}$ of 0.21 μM (page 46, line 11). Applicants state:

> [T]he data clearly indicated that the N-terminal domain of a-agglutinin interacted with the yeast cell surface in a ligand-dependent manner and therefore could be used as a tool for the development of yeast-based functional assays for G protein-coupled receptors. (page 46, lines 13-16)

Applicants' key insight was that the N-terminal domain of a-agglutinin can be used in yeast based functional assays to identify the ligands of G protein-coupled receptors. This insight is clearly missing from Wojciechowicz. Wojciechowicz merely describes the interaction of α-agglutinin and a-agglutinin. Wojciechowicz failed to recognize that this interaction could be used in methods of compound screening. In view of this failure, Wojciechowicz cannot teach or suggest such methods. In addition, because Wojciechowicz is silent as to screening assays and because there is nothing in Trueheart that would motivate one of ordinary skill in the art to seek a read out other than those disclosed in Trueheart, one of ordinary skill in the art would not be motivated to combine the references as suggested by the Examiner. Again, the Examiner has failed to supply any teaching or suggestion of the Applicants invention such that one of ordinary skill in the art would be motivated to combine the three references. Accordingly, the rejection of the claims over Trueheart and Capellaro in view of Wojciechowicz should also be withdrawn.

*Roy*

Roy describes the cloning of the Aga1 gene. In particular Roy describes a structure-functional analysis that employs genetic screens to identify yeast cells that include mutations in the Aga1 gene. Regarding these studies, Roy states, "On the basis of features of this gene and the secretion of active a-agglutinin binding subunit by agal mutants, we conclude that AGA1 encodes an a-agglutinin core subunit (Roy, page 4197, left column, 1st paragraph).
Like Cappellaro and Wojcicchowicz, Roy fails to teach or suggest compound-screening assays, much less using Aga1 in methods of compound screening. In the absence of such a teaching or suggestion, Roy fails to remedy the deficiencies of the other references.

*Wu, Alberts, Nare,* and *Reppert*

The remaining four references cited by the Examiner uniformly fail to mention the Aga2 gene or protein product, much less teach or suggest any method of compound screening that employs Aga2. In fact, the remaining references uniformly lack even the most tenuous connection with the claimed methods. Wu, Alberts, Nare, and Reppert are cited merely because they allegedly describe elements present in Applicants claims, *i.e.*, fluorescence polarization, antibodies, scintillation proximity assays, and a melatonin 1A receptor gene, respectively. The recitation of such disparate elements of the claims is insufficient to establish obviousness with respect to these references.

Applicants' claimed invention derives in part from Applicants' discovery of compound-screening methods using the Aga2 protein. Naturally, this discovery draws on methods existing in the art at the time the invention was made. However, the fact that individual elements present in Applicants' claims were also present in the cited art is not sufficient to establish *prima facie* obviousness.

The claimed invention ***cannot*** be assembled by picking and choosing elements from the prior art using the patentee's claim as a "blue print." There must be some ***reason*** for the combination other than the hindsight obtained from the invention itself. (*Interconnect* 774 F.2d 1132, at 1143 (*Fed Cir.* 1985) The Examiner has failed to supply that reason. In the absence of such a reason or motivation, the Examiner's rejections are nothing more than the result of hindsight reconstruction of the invention ***based solely on Applicants' teachings***.

In rejecting the pending claims for obviousness the Examiner has relied on no less than eight references. Applicants submit that such reliance belies the alleged obviousness of the claimed invention. *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1383 (*Fed. Cir.* 1986). "The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity." *Id.* at 1383. Although the number of references is not determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

In sum, none of the cited references, considered alone or in any combination, teaches or suggests all of the elements of Applicants' claimed invention. Specifically, none describes a method for identifying a test compound that modulates a heterologous receptor in a cell, where the method involves providing a cell which comprises a heterologous receptor that is functionally integrated into a signal transduction pathway of the cell, where cell surface presentation of a detectable signal comprising a protein product of the AGA2 gene is induced upon activation of the signal transduction pathway; contacting the cell with a test compound; and detecting the level of expression of AGA2 as a measure of the ability of the compound to modulate signaling via the heterologous receptor. Even if we accept *arguendo* that the individual elements of Applicants invention are present in the cited references, none of the references suggests the desirability of combining the various elements to arrive at Applicants' claimed invention and none suggests that if the combination were made that it would operate successfully. M.P.E.P. 2143. Accordingly, the obviousness rejection of the pending claims should be withdrawn.

**Claim Objections**

On page 16 of the Office Action, the Examiner indicates that claims 36 and 37 are objected to as being dependent upon a rejected claim. However, the Examiner says nothing more. Applicants respectfully request that the Examiner provide further clarification regarding the alleged claim objections.

## CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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